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ORIGINAL ARTICLE

Synthesis and antimicrobial activity of Schiff bases and 2-azetidinones derived from quinazolin-4(3*H*)-one

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Abstract A series of 2-oxo-azetidinyl-quinazolin-4(3*H*)-ones **5a**–**k** have been synthesized from Schiff bases **4a**–**k**. Schiff bases were synthesized by condensation reaction of compound **3** with substituted aromatic aldehydes. The benzoxazinone **2** was prepared by the cyclization reaction of acid chloride **1** with 5-bromo anthranilic acid. Further reaction of benzoxazinone **2** with hydrazine hydrate yielded compound **3**. The structures of synthesized compounds were elucidated on the basis of elemental analyses as well as IR and NMR spectral data. Schiff bases **4a**–**k** and 2-azetidinones **5a**–**k** were screened for antibacterial and antifungal activities *in vitro*. Compounds having chloro and methoxy group exhibited good antimicrobial activity.

1. Introduction

The heterocyclic compounds have great importance in medicinal chemistry. One of the most important heterocycle is quinazolinone possess wide spectrum of biological activities like antibacterial (Nanda et al., 2007), antifungal (Grover and Kini, 2006), anticonvulsant (Archana et al., 2004), anti-inflammatory (Kumar et al., 2007), antiviral (Saleh et al., 2002), hypolipidemic (Kurogi et al., 1996), antitubercular (Mosaad et al., 2004), CNS depressant (Jatav et al., 2008), antitumor (Cao et al., 2005), analgesic (Alagarsamy et al., 2007), antimalarial (Jiang et al., 2005) and antihistaminic (Alagarsamy et al., 2000). The 2-azetidinone ring system, a common structural feature of a number of wide spectrum β-lactam antibiotics, including penicillins, cephalosporins, carbapenems, nocardicins and monobactams, which have been widely used as chemotherapeutic agents to treat bacterial infections and microbial diseases. The 2-azetidinone derivatives have been reported to possess wide range of biological activities like antibacterial (Sharma et al., 1998), antifungal (Halve et al., 2007), anti-inflammatory (Gurupadayya et al., 2008), analgesic (Ishwar Bhat et al., 2003), anticonvulsant (Rajasekaran and Murugesan, 2005), anticancer (Veinberg and Vorona, 2004), and antitubercular (Kagthara et al., 2000). Biocidal activities of Schiff bases have been well established. These have been attributed to the toxophoric C═N linkage in them. Schiff base acquired broad spectrum biological activities like antibacterial (Iqbal et al.,

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2007), antifungal (Mishra et al., 2005), anti-inflammatory (Sharma et al., 2002), antiproliferative (Vicini et al., 2006), antitubercular (Lourenco et al., 2007) and anticonvulsant (Ragavendran et al., 2007).

Diclofenac is non-steroidal anti-inflammatory drug, often used to treat chronic pain associated with cancer, particularly if inflammation is also present. It has been found to be effective against all strains of multi-drug resistant *Escherichia coli*. Therefore, it may be suggested that diclofenac has the capacity to treat uncomplicated urinary tract infections caused by *E. coli* (Mazumdar et al., 2006). The diclofenac analogue compounds possess very good antibacterial activity (Dutta et al., 2000). The literature survey reveals that substitution of different heterocyclic moieties at 2nd or 3rd position of quinazolinone nucleus modulates the activity. In the present work we have synthesized some new derivatives of quinazolin-4(3*H*)-one of diclofenac analogue, containing 2-azetidinone at 3rd position and 2-[(2,6-dichlorophenyl)amino]benzyl unit from diclofenac at second position of quinazolin-4(3*H*)-one. The potency of schiff bases **4a**–**k** as well as 2-azetidinones **5a**–**k** were calculated against bacterial and fungal stains, and compared with reference drugs with hope to get better antimicrobial agents.

2. Experimental

2.1. General

Melting points were determined in one-end-open capillary tubes on a Mel-Temp apparatus and are uncorrected. Infrared (IR) absorption spectra were recorded on Perkin–Elmer RX-1 FTIR spectrometer using potassium bromide (KBr) pellet and the wave numbers were given in cm^{-1}. The ^1H NMR spectra were recorded in deutero chloroform ($CDCl_3$) on a Bruker Avance II 400 NMR spectrometer (400 MHz). The ^{13}C NMR spectra were recorded in deutero chloroform ($CDCl_3$) on a Bruker Avance II 400 NMR spectrometer operating at 100 MHz. The chemical shifts are reported in part per million (δ ppm) using tetramethylsilane (TMS) as an internal standard. The microanalyses were performed on a Carlo Erba 1108 elemental analyzer. The purities of the compounds were checked by thin layer chromatography (TLC) using ready-made silica gel plates (Merck) and benzene:methanol (8:2) as a solvent system. The spots were developed in an iodine chamber and visualized under ultraviolet (UV) lamp. 2-[(2,6-Dichlorophenyl)amino]phenyl acetyl chloride **1** was synthesized by the literature procedure (Furniss et al., 1989).

2.2. Synthesis of 6-bromo-2-[2-(2,6-dichlorophenyl)amino]benzyl-4H-3,1-benzoxazin-4-one (2)

A mixture of 2-[(2,6-dichlorophenyl)amino]phenyl acetyl chloride **1** (0.02 mol) and 5-bromo anthranilic acid (0.02 mol) in pyridine (40 ml) was stirred at 0–5 °C for 1 h, further stirred for 1 h at room temperature. A pasty mass obtained which was washed thoroughly with sodium bicarbonate (5%) to remove unreacted acid. A solid separated was filtered, dried and recrystallized from methanol.

Yield 55%, m.p. 194–198 °C. IR (KBr): t = 3446 (NH), 2926, 2850 (CH_2), 1740 (C═O), 1618 (C═N), 1153 (C–O), 743 (C–Cl), 565 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.53 (s, 2H, CH_2), 6.38–8.16 (m, 10H, Ar–*H*), 9.10 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 32.43 (*C*H_2), 116.31, 118.64, 120.62, 121.67, 124.31, 124.57, 126.54, 127.17, 127.43, 129.41, 131.12, 135.22, 137.29, 138.23, 141.78, 148.73 (Ar–*C*), 159.23 (*C*═O), 164.33 (*C*═N) ppm. Anal. For $C_{21}H_{13}BrCl_2N_2O_2$ (476.15) calcd. C52.97, H2.75, N5.88. Found C52.94, H2.71, N5.92.

2.3. Synthesis of 3-amino-6-bromo-2-[2-(2,6-dichlorophenyl)amino]benzyl-quinazolin-4(3H)-one (3)

A mixture of **2** (0.01 mol) and hydrazine hydrate (0.02 mol) in absolute methanol (20 ml) was refluxed on water bath for 4–6 h, excess of solvent was distilled off and the residue was cooled whereupon a crystalline solid was separated out, which was recrystallized from methanol.

Yield 58%, m.p. 178–182 °C. IR (KBr): t = 3495–3405 (NH and NH_2), 2922, 2848 (CH_2), 1684 (C═O), 1610 (C═N), 755 (C–Cl), 570 (C–Br). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.56 (s, 2H, CH_2), 5.75 (bs, 2H, NH_2), 6.39–8.15 (m, 10H, Ar–*H*), 9.15 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 30.57 (*C*H_2), 116.14, 120.45, 121.52, 123.14, 124.23, 124.55, 126.74, 127.28, 127.49, 129.36, 131.13, 132.22, 136.45, 137.26, 141.78, 146.22 (Ar–*C*), 161.28 (*C*═O), 164.53 (*C*═N) ppm. Anal. For $C_{21}H_{15}BrCl_2N_4O$ (490.18) calcd. C51.46, H3.08, N11.43. Found C51.38, H3.02, N11.39.

2.4. General procedure for the synthesis of Schiff bases (4a–k)

To a mixture of **3** (0.005 mol) and substituted aromatic aldehydes (0.005 mol) in absolute ethanol (40 ml) was added few drops of glacial acetic acid. Then the mixture was refluxed on water bath for 5–6 h. The excess of solvent was distilled off, poured onto ice cold water. The separated solid was filtered, washed and recrystallized from ethanol.

2.4.1. 6-Bromo-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-(2-nitrobenzylideneamino)-quinazolin-4(3H)-one (4a)

Yield 58%, m.p. 163–167 °C. IR (KBr): t = 3432 (NH), 2918, 2843 (CH_2), 1675 (C═O, quinazolinone), 1634 (N═CH), 1612 (C═N), 1550, 1362 (NO_2), 755 (C–Cl), 585 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.54 (s, 2H, CH_2), 6.23 (s, 1H, N═C*H*), 6.37–8.15 (m, 14H, Ar–*H*), 9.15 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 33.42 (*C*H_2), 116.19, 120.47, 121.45, 123.11, 123.82, 124.30, 124.68, 126.73, 127.26, 127.41, 128.54, 129.35, 130.26, 131.17, 131.93, 132.12, 135.47, 136.42, 137.25, 141.83, 146.34, 148.67 (Ar–*C*), 144.25 (N═*C*H), 159.22 (*C*═O), 164.46 (*C*═N) ppm. Anal. For $C_{28}H_{18}BrCl_2N_5O_3$ (623.28) calcd. C53.96, H2.91, N11.24. Found C53.88, H2.86, N11.17.

2.4.2. 6-Bromo-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-(3-nitrobenzylideneamino)-quinazolin-4(3H)-one (4b)

Yield 53%, m.p. 150–156 °C. IR (KBr): t = 3435 (NH), 2920, 2850 (CH_2), 1677 (C═O, quinazolinone), 1635 (N═CH), 1615 (C═N), 1553, 1365 (NO_2), 744 (C–Cl), 578 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.55 (s, 2H, CH_2), 6.25 (s, 1H, N═C*H*), 6.38–8.39 (m, 14H, Ar–*H*), 9.14 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 33.52 (*C*H_2), 116.07, 120.54, 121.56, 122.64, 123.23, 124.32, 124.48, 125.87, 126.81, 127.27, 127.36, 129.44,

129.53, 131.18, 132.29, 133.92, 134.83, 136.44, 137.17, 141.76, 146.24, 149.16 (Ar–*C*), 144.16 (N=*C*H), 159.43 (*C*=O), 164.34 (*C*=N) ppm. Anal. For $C_{28}H_{18}BrCl_2N_5O_3$ (623.28) calcd. C53.96, H2.91, N11.24. Found C53.85, H2.95, N11.19.

*2.4.3. 6-Bromo-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-(2-hydroxybenzylideneamino)-quinazolin-4(3H)-one (**4c**)*

Yield 52%, m.p. 155–159 °C. IR (KBr): t = 3445 (NH), 3255 (OH), 2925, 2852 (CH_2), 1685 (C=O, quinazolinone), 1628 (N=CH), 1612 (C=N), 745 (C–Cl), 575 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.60 (s, 2H, CH_2), 5.65 (bs, 1H, O*H*), 6.22 (s, 1H, N=C*H*), 6.37–8.16 (m, 14H, Ar–*H*), 9.13 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 33.67 (*C*H_2), 114.53, 116.22, 117.89, 120.55, 121.25, 121.53, 123.17, 124.33, 124.52, 126.72, 127.22, 127.55, 129.51, 130.43, 131.21, 132.23, 133.12, 136.45, 137.15, 141.72, 146.26, 158.84 (Ar–*C*), 143.92 (N=*C*H), 159.38 (*C*=O), 164.25 (*C*=N) ppm. Anal. For $C_{28}H_{19}BrCl_2N_4O_2$ (594.29) calcd. C56.59, H3.22, N9.43. Found C56.48, H3.16, N9.51.

*2.4.4. 6-Bromo-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-(4-hydroxybenzylideneamino)-quinazolin-4(3H)-one (**4d**)*

Yield 54%, m.p. 163–168 °C. IR (KBr): t = 3440 (NH), 3250 (OH), 2923, 2842 (CH_2), 1680 (C=O, quinazolinone), 1635 (N=CH), 1608 (C=N), 749 (C–Cl), 582 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.58 (s, 2H, CH_2), 5.60 (bs, 1H, O*H*), 6.20 (s, 1H, N=C*H*), 6.38–8.14 (m, 14H, Ar–*H*), 9.20 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 33.47 (*C*H_2), 114.23, 116.32, 120.66, 121.65, 123.05, 124.34, 124.56, 125.67, 126.73, 127.29, 127.58, 129.45, 130.36, 131.21, 132.12, 136.49, 137.27, 141.68, 146.19, 158.63 (Ar–*C*), 143.87 (N=*C*H), 159.26 (*C*=O), 164.46 (*C*=N) ppm. Anal. For $C_{28}H_{19}BrCl_2N_4O_2$ (594.29) calcd. C56.59, H3.22, N9.43. Found C56.51, H3.17, N9.38.

*2.4.5. 6-Bromo-3-(2-chlorobenzylideneamino)-2-[2-(2,6-dichlorophenyl)amino]benzyl-quinazolin-4(3H)-one (**4e**)*

Yield 58%, m.p. 140–146 °C. IR (KBr): t = 3449 (NH), 2916, 2845 (CH_2), 1674 (C=O, quinazolinone), 1631 (N=CH), 1614 (C=N), 743 (C–Cl), 570 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.55 (s, 2H, CH_2), 6.21 (s, 1H, N=C*H*), 6.37–8.15 (m, 14H, Ar–*H*), 9.17 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 33.23 (*C*H_2), 116.12, 120.47, 121.63, 123.10, 124.27, 124.44, 126.72, 126.93, 127.23, 127.43, 128.23, 129.42, 130.52, 131.15, 132.17, 132.86, 134.48, 135.12, 136.54, 137.26, 141.73, 146.12 (Ar–*C*), 144.08 (N=*C*H), 159.46 (*C*=O), 164.35 (*C*=N) ppm. Anal. For $C_{28}H_{18}BrCl_3N_4O$ (612.73) calcd. C54.89, H2.96, N9.14. Found C54.78, H2.87, N9.10.

*2.4.6. 6-Bromo-3-(4-chlorobenzylideneamino)-2-[2-(2,6-dichlorophenyl)amino]benzyl-quinazolin-4(3H)-one (**4f**)*

Yield 55%, m.p. 154–161 °C. IR (KBr): t = 3448 (NH), 2926, 2855 (CH_2), 1678 (C=O, quinazolinone), 1635 (N=CH), 1617 (C=N), 754 (C–Cl), 575 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.52 (s, 2H, CH_2), 6.23 (s, 1H, N=C*H*), 6.40–8.16 (m, 14H, Ar–*H*), 9.14 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 33.32 (*C*H_2), 116.10, 120.55, 121.56, 123.19, 124.23, 124.58, 126.83, 127.22, 127.46, 128.62, 129.47, 130.24, 131.14, 132.26, 133.35, 136.42, 136.86, 137.28, 141.85, 146.28 (Ar–*C*), 144.12 (N=*C*H), 159.36 (*C*=O), 164.48 (*C*=N) ppm. Anal. For $C_{28}H_{18}BrCl_3N_4O$ (612.73) calcd. C54.89, H2.96, N9.14. Found C54.82, H2.90, N9.19.

*2.4.7. 6-Bromo-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-(4-methoxybenzylideneamino)-quinazolin-4(3H)-one (**4g**)*

Yield 56%, m.p. 160–166 °C. IR (KBr): t = 3435 (NH), 2924, 2850 (CH_2), 1672 (C=O, quinazolinone), 1637 (N=CH), 1607 (C=N), 1204, 1106 (C–O–C), 757 (C–Cl), 582 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.58 (s, 2H, CH_2), 3.62 (s, 3H, OCH_3), 6.19 (s, 1H, N=C*H*), 6.37–8.14 (m, 14H, Ar–*H*), 9.16 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 33.52 (*C*H_2), 53.68 (O*C*H_3), 113.38, 116.05, 120.50, 121.46, 123.14, 124.35, 124.66, 125.73, 126.79, 127.18, 127.36, 129.35, 130.46, 131.15, 132.17, 136.45, 137.20, 141.79, 146.38, 161.37 (Ar–*C*), 144.37 (N=*C*H), 159.25 (*C*=O), 164.31 (*C*=N) ppm. Anal. For $C_{29}H_{21}BrCl_2N_4O_2$ (608.31) calcd. C57.26, H3.48, N9.21. Found C57.15, H3.39, N9.15.

*2.4.8. 6-Bromo-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-(3,4,5-trimethoxybenzylideneamino)-quinazolin-4(3H)-one (**4h**)*

Yield 54%, m.p. 162–168 °C. IR (KBr): t = 3440 (NH), 2926, 2852 (CH_2), 1675 (C=O, quinazolinone), 1633 (N=CH), 1610 (C=N), 1203, 1102 (C–O–C), 741 (C–Cl), 567 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.55 (s, 2H, CH_2), 3.65 (s, 9H, (OCH_3)$_3$), 6.25 (s, 1H, N=C*H*), 6.36–8.15 (m, 12H, Ar–*H*), 9.14 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 33.59 (*C*H_2), 55.76 (O*C*H_3), 55.38 (O*C*H_3), 110.15, 116.23, 120.54, 121.53, 123.22, 124.35, 124.45, 126.87, 127.24, 127.56, 128.32, 129.43, 131.20, 132.26, 136.52, 137.17, 141.75, 142.17, 146.17, 149.46 (Ar–*C*), 144.29 (N=*C*H), 159.63 (*C*=O), 164.43 (*C*=N) ppm. Anal. For $C_{31}H_{25}BrCl_2N_4O_4$ (668.36) calcd. C55.71, H3.77, N8.38. Found C55.80, H3.69, N8.32.

*2.4.9. 6-Bromo-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-(2-hydroxy-4-methoxybenzylideneamino)-quinazolin-4(3H)-one (**4i**)*

Yield 56%, m.p. 150–155 °C. IR (KBr): t = 3443 (NH), 3252 (OH), 2923, 2853 (CH_2), 1682 (C=O, quinazolinone), 1637 (N=CH), 1612 (C=N), 1207, 1100 (C–O–C), 753 (C–Cl), 580 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.56 (s, 2H, CH_2), 3.65 (s, 3H, OCH_3), 5.62 (bs, 1H, O*H*), 6.18 (s, 1H, N=C*H*), 6.39–8.13 (m, 13H, Ar–*H*), 9.18 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 33.54 (*C*H_2), 52.43 (O*C*H_3), 98.68, 105.13, 107.86, 116.16, 120.55, 121.56, 123.12, 124.34, 124.52, 126.82, 127.22, 127.44, 129.47, 131.19, 131.83, 132.24, 136.46, 137.23, 141.82, 146.31, 157.77, 161.26 (Ar–*C*), 144.18 (N=*C*H), 159.16 (*C*=O), 164.56 (*C*=N) ppm. Anal. For $C_{29}H_{21}BrCl_2N_4O_3$ (624.31) calcd. C55.79, H3.39, N8.97. Found C55.66, H3.34, N8.91.

*2.4.10. 6-Bromo-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-[4-(dimethylamino)benzylideneamino]-quinazolin-4(3H)-one (**4j**)*

Yield 50%, m.p. 158–163 °C. IR (KBr): t = 3448 (NH), 2922, 2849 (CH_2), 1678 (C=O, quinazolinone), 1635 (N=CH), 1613 (C=N), 744 (C–Cl), 568 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.84 (s, 6H, N(CH_3)$_2$), 3.57 (s,

2H, CH_2), 6.25 (s, 1H, N=CH), 6.37–8.12 (m, 14H, Ar–H), 9.14 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 33.72 (CH_2), 42.58 (N(CH_3)$_2$), 111.83, 116.25, 120.45, 121.56, 123.05, 123.76, 124.33, 124.42, 126.90, 127.16, 127.56, 129.37, 130.32, 131.24, 132.19, 136.53, 137.18, 141.95, 146.27, 149.34 (Ar–C), 143.95 (N=CH), 159.64 (C=O), 164.37 (C=N) ppm. Anal. For $C_{30}H_{24}BrCl_2N_5O$ (621.35) calcd. C57.99, H3.89, N11.27. Found C57.89, H3.97, N11.34.

*2.4.11. 6-Bromo-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-[4-(diethylamino)-2-hydroxybenzylideneamino]-quinazolin-4(3H)-one (**4k**)*

Yield 60%, m.p. 156–162 °C. IR (KBr): t = 3445 (NH), 3260 (OH), 2922, 2850 (CH_2), 1679 (C=O, quinazolinone), 1636 (N=CH), 1605 (C=N), 758 (C–Cl), 592 (C–Br) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.34 (t, 6H, N(CH$_2$CH_3)$_2$, J = 7.6 Hz), 2.82 (q, 4H, N(CH_2CH$_3$)$_2$, J = 7.6 Hz), 3.56 (s, 2H, CH_2), 5.66 (s, 1H, OH), 6.22 (s, 1H, N=CH), 6.38–8.16 (m, 13H, Ar–H), 9.18 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 14.56 (N(CH$_2$CH_3)$_2$), 33.42 (CH_2), 43.74 (N(CH_2CH$_3$)$_2$), 97.16, 105.12, 105.43, 116.29, 120.47, 121.57, 123.13, 124.34, 124.46, 126.92, 127.16, 127.53, 129.37, 131.23, 131.67, 132.19, 136.55, 137.20, 141.93, 146.11, 150.27, 158.46 (Ar–C), 144.05 (N=CH), 159.55 (C=O), 164.46 (C=N) ppm. Anal. For $C_{32}H_{28}BrCl_2N_5O_2$ (665.41) calcd. C57.76, H4.24, N10.52. Found C57.68, H4.18, N10.56.

*2.5. General procedure for the synthesis of 2-azetidinones (**5a–k**)*

A solution of **4a–k** (0.0025 mol) in dry dioxane (20 ml) was added to a well stirred mixture of chloro acetyl chloride (0.0025 mol) and triethylamine (0.0025 mol) in dry dioxane (20 ml) at 0–5 °C. The reaction mixture was stirred for 10–12 h and kept for two days at room temperature. The product was isolated and recrystallized from ethanol.

*2.5.1. 6-Bromo-3-[3-chloro-4-(2-nitrophenyl)-2-oxoazetidin-1-yl]-2-[2-(2,6-dichloro phenyl)amino]benzyl-quinazolin-4(3H)-one (**5a**)*

Yield 54%, m.p. 178–183 °C. IR (KBr): t = 3425 (NH), 2919, 2845 (CH_2), 1751 (C=O, azetidinone), 1675 (C=O, quinazolinone), 1613 (C=N), 1556, 1365 (NO_2), 754 (C–Cl), 570 (C–Br) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.28 (d, 1H, N–CH, J = 5.2 Hz), 3.35 (d, 1H, CH–Cl, J = 5.2 Hz), 3.55 (s, 2H, CH_2), 6.38–8.15 (m, 14H, Ar–H), 9.15 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 31.46 (CH_2), 54.28 (N–CH), 65.44 (CH–Cl), 116.21, 120.46, 121.37, 123.16, 123.52, 124.23, 124.72, 126.78, 127.31, 127.43, 128.12, 128.54, 129.32, 131.25, 132.18, 135.37, 136.45, 136.78, 137.16, 141.88, 146.32, 148.43 (Ar–C), 161.46 (C=O, quinazolinone), 161.88 (C=O, azetidinone), 164.32 (C=N) ppm. Anal. For $C_{30}H_{19}BrCl_3N_5O_4$ (699.77) calcd. C51.49, H2.74, N10.01. Found C51.42, H2.70, N9.95.

*2.5.2. 6-Bromo-3-[3-chloro-4-(3-nitrophenyl)-2-oxoazetidin-1-yl]-2-[2-(2,6-dichloro phenyl)amino]benzyl-quinazolin-4(3H)-one (**5b**)*

Yield 56%, m.p. 155–161 °C. IR (KBr): t = 3418 (NH), 2917, 2842 (CH_2), 1748 (C=O, azetidinone), 1673 (C=O, quinazolinone), 1612 (C=N), 1558, 1364 (NO_2), 742 (C–Cl), 579 (C–Br) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.23 (d, 1H, N–CH, J = 5.3 Hz), 3.34 (d, 1H, CH–Cl, J = 5.3 Hz), 3.53 (s, 2H, CH_2), 6.38–8.40 (m, 14H, Ar–H), 9.16 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 31.57 (CH_2), 57.32 (N–CH), 62.68 (CH–Cl), 116.15, 119.86, 120.53, 121.46, 122.87, 123.34, 124.23, 124.53, 126.84, 127.28, 127.47, 129.43, 130.05, 131.16, 132.24, 134.72, 136.47, 137.22, 141.85, 142.46, 146.29, 148.18 (Ar–C), 161.37 (C=O, quinazolinone), 161.96 (C=O, azetidinone), 164.65 (C=N) ppm. Anal. For $C_{30}H_{19}BrCl_3N_5O_4$ (699.77) calcd. C51.49, H2.74, N10.01. Found C51.58, H2.67, N9.94.

*2.5.3. 6-Bromo-3-[3-chloro-4-(2-hydroxyphenyl)-2-oxoazetidin-1-yl]-2-[2-(2,6-dichlorophenyl)amino]benzyl-quinazolin-4(3H)-one (**5c**)*

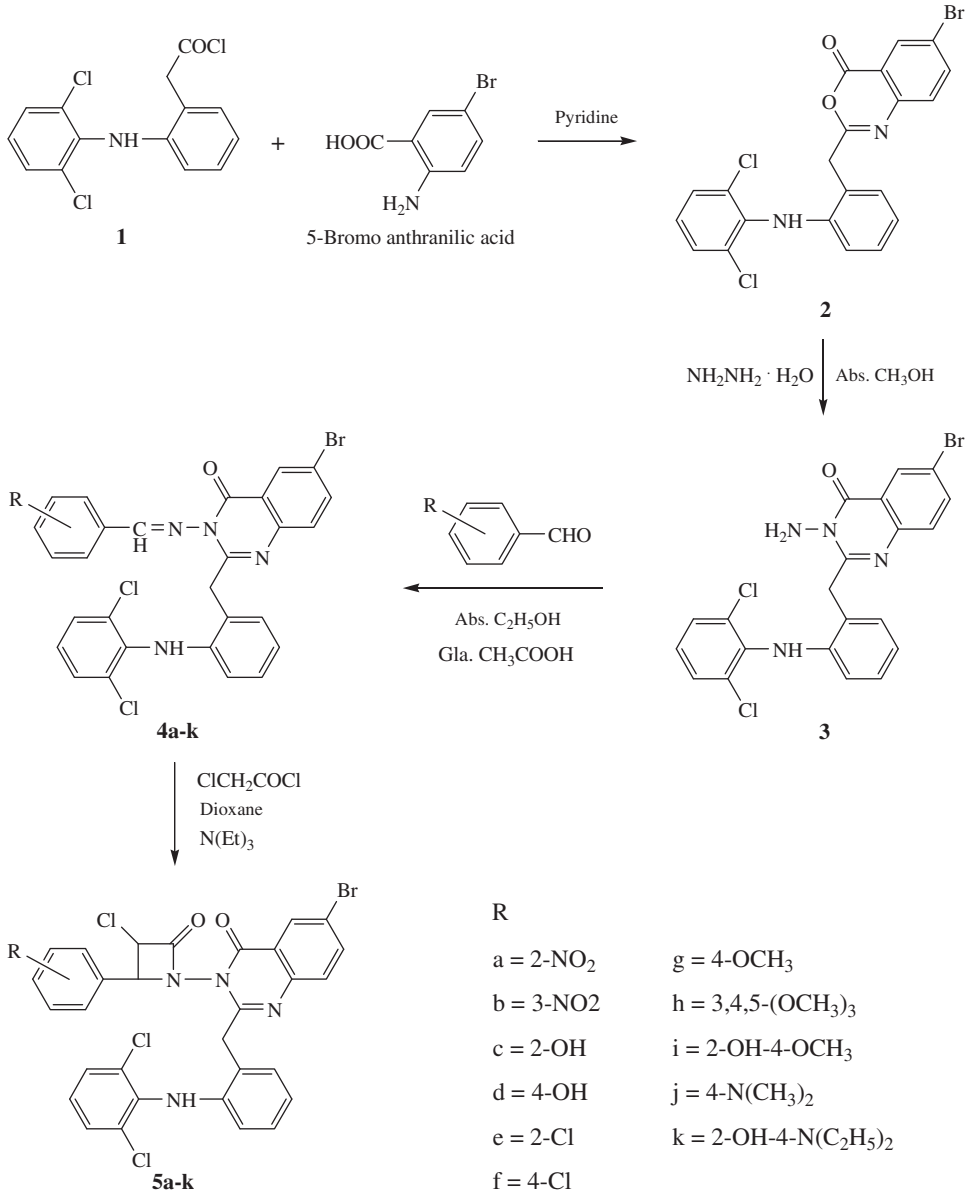
Yield 51%, m.p. 160–166 °C. IR (KBr): t = 3440 (NH), 3260 (OH), 2920, 2845 (CH_2), 1750 (C=O, azetidinone), 1675 (C=O, quinazolinone), 1610 (C=N), 745 (C–Cl), 573 (C–Br) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.30 (d, 1H, N–CH, J = 5.2 Hz), 3.38 (d, 1H, CH–Cl, J = 5.2 Hz), 3.59 (s, 2H, CH_2), 5.64 (bs, 1H, OH), 6.38–8.15 (m, 14H, Ar–H), 9.14 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 31.63 (CH_2), 55.65 (N–CH), 63.48 (CH–Cl), 113.17, 116.19, 120.46, 120.78, 121.64, 123.28, 124.23, 124.42, 126.78, 127.22, 127.47, 128.36, 128.84, 129.49, 129.76, 131.13, 132.35, 136.57, 137.25, 141.83, 146.32, 156.42 (Ar–C), 161.34 (C=O, quinazolinone), 161.56 (C=O, azetidinone), 164.53 (C=N) ppm. Anal. For $C_{30}H_{20}BrCl_3N_4O_3$ (670.77) calcd. C53.72, H3.01, N8.35. Found C53.64, H2.92, N8.28.

*2.5.4. 6-Bromo-3-[3-chloro-4-(4-hydroxyphenyl)-2-oxoazetidin-1-yl]-2-[2-(2,6-dichlorophenyl)amino]benzyl-quinazolin-4(3H)-one (**5d**)*

Yield 62%, m.p. 165–170 °C. IR (KBr): t = 3443 (NH), 3255 (OH), 2923, 2852 (CH_2), 1751 (C=O, azetidinone), 1677 (C=O, quinazolinone), 1613 (C=N), 757 (C–Cl), 566 (C–Br) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.29 (d, 1H, N–CH, J = 5.5 Hz), 3.40 (d, 1H, CH–Cl, J = 5.5 Hz), 3.59 (s, 2H, CH_2), 5.62 (bs, 1H, OH), 6.37–8.15 (m, 14H, Ar–H), 9.18 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 31.52 (CH_2), 58.78 (N–CH), 66.73 (CH–Cl), 114.52, 116.23, 120.46, 121.56, 123.12, 124.32, 124.68, 126.83, 127.33, 127.50, 129.52, 130.18, 131.13, 132.26, 134.89, 136.42, 137.26, 141.95, 146.23, 157.93 (Ar–C), 161.52 (C=O, quinazolinone), 161.78 (C=O, azetidinone), 164.29 (C=N) ppm. Anal. For $C_{30}H_{20}BrCl_3N_4O_3$ (670.77) calcd. C53.72, H3.01, N8.35. Found C53.81, H2.95, N8.38.

*2.5.5. 6-Bromo-3-[3-chloro-4-(2-chlorophenyl)-2-oxoazetidin-1-yl]-2-[2-(2,6-dichlorophenyl)amino]benzyl-quinazolin-4(3H)-one (**5e**)*

Yield 58%, m.p. 167–173 °C. IR (KBr): t = 3449 (NH), 2918, 2846 (CH_2), 1745 (C=O, azetidinone), 1675 (C=O, quinazolinone), 1614 (C=N), 744 (C–Cl), 580 (C–Br) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.25 (d, 1H, N–CH, J = 5.3 Hz), 3.37 (d, 1H, CH–Cl, J = 5.3 Hz), 3.58 (s, 2H, CH_2), 6.36–8.16 (m, 14H, Ar–H), 9.16 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 31.74 (CH_2), 56.62 (N–CH), 65.54 (CH–Cl), 116.21, 120.54, 121.55, 123.19, 124.23, 124.38, 125.53, 126.82, 127.29, 127.44, 127.85, 128.26, 128.87, 129.48, 131.15, 132.24, 134.16, 136.65, 137.27,



Scheme 1

141.76, 142.38, 146.06 (Ar–*C*), 161.35 (*C*═O, quinazolinone), 161.73 (*C*═O, azetidinone), 164.34 (*C*═N) ppm. Anal. For $C_{30}H_{19}BrCl_4N_4O_2$ (689.21) calcd. C52.28, H2.78, N8.13. Found C52.23, H2.76, N8.07.

*2.5.6. 6-Bromo-3-[3-chloro-4-(4-chlorophenyl)-2-oxoazetidin-1-yl]-2-[2-(2,6-dichlorophenyl)amino]benzyl-quinazolin-4(3H)-one (**5f**)*

Yield 65%, m.p. 173–180 °C. IR (KBr): t = 3450 (NH), 2921, 2853 (CH_2), 1747 (C═O, azetidinone), 1684 (C═O, quinazolinone), 1617 (C═N), 760 (C–Cl), 585 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.24 (d, 1H, N–C*H*, J = 5.5 Hz), 3.35 (d, 1H, C*H*–Cl, J = 5.5 Hz), 3.53 (s, 2H, CH_2), 6.41–8.15 (m, 14H, Ar–*H*), 9.13 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 31.37 (*C*H_2), 58.66 (N–*C*H), 63.62 (*C*H–Cl), 116.15, 120.43, 121.43, 123.12, 124.35, 124.53, 126.84, 127.23, 127.47, 128.17, 128.48, 129.44, 131.13, 132.36, 132.67, 136.52, 137.26, 141.81, 142.23, 146.15 (Ar–*C*), 161.26 (*C*═O, quinazolinone), 162.04 (*C*═O, azetidinone), 164.51 (*C*═N) ppm. Anal. For $C_{30}H_{19}BrCl_4N_4O_2$ (689.21) calcd. C52.28, H2.78, N8.13. Found C52.40, H2.75, N8.09.

*2.5.7. 6-Bromo-3-[3-chloro-4-(4-methoxyphenyl)-2-oxoazetidin-1-yl]-2-[2-(2,6-dichlorophenyl)amino]benzyl-quinazolin-4(3H)-one (**5g**)*

Yield 62%, m.p. 152–156 °C. IR (KBr): t = 3422 (NH), 2930, 2855 (CH_2), 1748 (C═O, azetidinone), 1672 (C═O, quinazolinone), 1612 (C═N), 1212, 1108 (C–O–C), 755 (C–Cl), 595 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.25 (d, 1H, N–C*H*, J = 5.3 Hz), 3.36 (d, 1H, C*H*–Cl, J = 5.3 Hz), 3.56 (s, 2H, CH_2), 3.63 (s, 3H, OCH_3), 6.38–8.14 (m, 14H, Ar–*H*), 9.15 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 31.26 (*C*H_2), 53.76 (O*C*H_3), 58.57 (N–*C*H), 64.43 (*C*H–Cl), 113.32, 116.18, 120.41, 121.37, 123.26, 124.28, 124.55, 126.79, 127.25, 127.48, 128.23, 129.42, 131.16,

Table 1 Gram positive antibacterial activity of compounds **4a–k** and **5a–k**.

Compound	R	*S. aureus* ATCC 9144				Potency (%)	*B. subtilis* ATCC 6633				Potency (%)
		Std.: penicillin-G					Std.: penicillin-G				
		U_H	U_L	S_H	S_L		U_H	U_L	S_H	S_L	
4a	2-NO_2	3	2	12	8	29.60	4	3	15	9	28.92
4b	3-NO_2	2	1	12	7	23.76	2	2	15	9	18.22
4c	2-OH	4	2	12	8	38.83	4	3	15	9	28.92
4d	4-OH	3	3	12	8	24.19	3	2	15	9	24.99
4e	2-Cl	6	3	12	8	52.88	5	3	15	9	36.00
4f	4-Cl	6	4	12	8	50.88	8	5	15	9	53.56
4g	4-OCH_3	6	4	12	8	50.88	9	5	15	9	60.00
4h	3,4,5-$(OCH_3)_3$	6	5	12	8	48.20	8	5	15	9	53.56
4i	2-OH-4-OCH_3	6	5	12	8	48.20	6	4	16	9	38.33
4j	4-$N(CH_3)_2$	0	0	12	8	0	0	0	15	9	0
4k	2-OH-4-$N(C_2H_5)_2$	0	0	12	8	0	0	0	15	9	0
5a	2-NO_2	3	2	12	8	29.63	5	4	15	9	33.47
5b	3-NO_2	4	0	12	8	44.44	3	3	15	9	21.60
5c	2-OH	4	2	12	8	38.83	3	3	15	9	21.60
5d	4-OH	5	2	12	8	47.09	6	3	15	9	42.68
5e	2-Cl	4	2	13	8	35.33	4	3	15	9	28.92
5f	4-Cl	6	5	12	8	48.20	8	5	15	9	53.56
5g	4-OCH_3	6	4	12	8	50.88	9	5	15	9	60.00
5h	3,4,5-$(OCH_3)_3$	6	4	12	8	50.88	7	4	15	9	47.81
5i	2-OH-4-OCH_3	4	3	12	8	34.85	6	4	15	9	40.90
5j	4-$N(CH_3)_2$	0	0	12	7	0	1	0	15	8	0
5k	2-OH-4-$N(C_2H_5)_2$	0	0	12	8	0	0	0	15	9	0

U_H: zone of inhibition of compound at 100 μg/ml; U_L: zone of inhibition of compound at 50 μg/ml; S_H: zone of inhibition of standard at 100 μg/ml; S_L: zone of inhibition of standard at 50 μg/ml.

Table 2 Gram negative antibacterial activity of compounds **4a–k** and **5a–k**.

Compound	R	*P. aeruginosa* ATCC 9027				Potency (%)	*E. coli* ATCC 25922				Potency (%)
		Std.: penicillin-G					Std.: penicillin-G				
		U_H	U_L	S_H	S_L		U_H	U_L	S_H	S_L	
4a	2-NO_2	3	2	13	8	27.40	3	2	14	9	26.57
4b	3-NO_2	2	1	12	8	25.19	3	2	14	9	26.57
4c	2-OH	3	2	12	8	29.63	4	4	14	9	26.57
4d	4-OH	4	2	12	7	36.75	3	3	14	8	22.49
4e	2-Cl	5	3	12	8	44.44	5	3	14	9	38.80
4f	4-Cl	7	5	12	8	58.24	6	5	14	9	41.33
4g	4-OCH_3	7	5	12	8	58.24	8	6	14	9	56.66
4h	3,4,5-$(OCH_3)_3$	7	5	12	8	58.24	7	5	14	9	49.94
4i	2-OH-4-OCH_3	4	3	12	8	34.85	5	3	14	9	38.80
4j	4-$N(CH_3)_2$	0	0	12	7	0	0	0	14	9	0
4k	2-OH-4-$N(C_2H_5)_2$	0	0	12	8	0	0	0	15	9	0
5a	2-NO_2	5	2	12	8	47.09	4	3	14	9	30.78
5b	3-NO_2	4	3	12	7	34.03	4	3	14	9	30.78
5c	2-OH	5	3	12	8	44.44	4	2	14	9	34.20
5d	4-OH	6	3	12	8	52.88	5	3	14	9	38.80
5e	2-Cl	3	2	12	8	29.63	4	2	14	9	34.20
5f	4-Cl	7	5	12	8	58.24	7	5	14	9	49.94
5g	4-OCH_3	8	5	13	8	61.54	9	5	14	9	64.29
5h	3,4,5-$(OCH_3)_3$	7	5	12	8	58.24	7	4	15	8	47.03
5i	2-OH-4-OCH_3	4	3	12	8	34.85	6	4	14	9	44.02
5j	4-$N(CH_3)_2$	0	0	12	8	0	1	0	14	9	0
5k	2-OH-4-$N(C_2H_5)_2$	0	0	12	8	0	0	0	14	9	0

U_H: zone of inhibition of compound at 100 μg/ml; U_L: zone of inhibition of compound at 50 μg/ml; S_H: zone of inhibition of standard at 100 μg/ml; S_L: zone of inhibition of standard at 50 μg/ml.

132.21, 134.37, 136.56, 137.22, 141.75, 146.27, 160.12 (Ar–*C*), 161.57 (*C*═O, quinazolinone), 162.12 (*C*═O, azetidinone), 164.56 (*C*═N) ppm. Anal. For $C_{31}H_{22}BrCl_3N_4O_3$ (684.79) calcd. C54.37, H3.24, N8.18. Found C54.29, H3.14, N8.12.

*2.5.8. 6-Bromo-3-[3-chloro-4-(3,4,5-trimethoxyphenyl)-2-oxoazetidin-1-yl]-2-[2-(2,6-dichlorophenyl)amino]benzyl-quinazolin-4(3H)-one (**5h**)*

Yield 57%, m.p. 167–175 °C. IR (KBr): t = 3420 (NH), 2925, 2840 (CH_2), 1745 (C═O, azetidinone), 1668 (C═O, quinazolinone), 1610 (C═N), 1210, 1105 (C–O–C), 750 (C–Cl), 565 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.24 (d, 1H, N–C*H*, J = 5.2 Hz), 3.34 (d, 1H, C*H*–Cl, J = 5.2 Hz), 3.54 (s, 2H, CH_2), 3.64 (s, 9H, (OCH_3)$_3$), 6.37–8.16 (m, 12H, Ar–*H*), 9.13 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 31.42 (*C*H_2), 55.67 (OCH_3), 55.24 (O*C*H_3), 61.73 (N–*C*H), 64.36 (*C*H–Cl), 108.36, 116.14, 120.51, 121.66, 123.35, 124.32, 124.51, 126.73, 127.28, 127.44, 129.36, 131.11, 132.19, 136.58, 137.23, 139.18, 140.16, 141.83, 146.24, 149.73 (Ar–*C*), 161.64 (*C*═O, quinazolinone), 162.06 (*C*═O, azetidinone), 164.47 (*C*═N) ppm. Anal. For $C_{33}H_{26}BrCl_3N_4O_5$ (744.85) calcd. C53.21, H3.52, N7.52. Found C53.12, H3.59, N7.47.

*2.5.9. 6-Bromo-3-[3-chloro-4-(2-hydroxy-4-methoxyphenyl)-2-oxoazetidin-1-yl]-2-[2-(2,6-dichlorophenyl)amino]benzyl-quinazolin-4(3H)-one (**5i**)*

Yield 53%, m.p. 168–174 °C. IR (KBr): t = 3428 (NH), 3257 (OH), 2927, 2853 (CH_2), 1752 (C═O, azetidinone), 1679 (C═O, quinazolinone), 1614 (C═N), 1208, 1104 (C–O–C), 749 (C–Cl), 573 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.27 (d, 1H, N–C*H*, J = 5.5 Hz), 3.36 (d, 1H, C*H*–Cl, J = 5.5 Hz), 3.55 (s, 2H, CH_2), 3.63 (s, 3H, OCH_3), 5.61 (bs, 1H, O*H*), 6.39–8.14 (m, 13H, Ar–*H*), 9.17 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 31.35 (*C*H_2), 52.56 (OCH_3), 54.82 (N–*C*H), 64.63 (*C*H–Cl), 97.86, 104.97, 116.12, 120.54, 121.43, 122.86, 123.18, 124.32, 124.46, 126.84, 127.31, 127.37, 128.53, 129.44, 131.19, 132.34, 136.58, 137.22, 141.76, 146.47, 156.34, 158.78 (Ar–*C*), 161.55 (*C*═O, quinazolinone), 161.98 (*C*═O, azetidinone), 164.59 (*C*═N) ppm. Anal. For $C_{31}H_{22}BrCl_3N_4O_4$ (700.79) calcd. C53.13, H3.16, N7.99. Found C53.02, H3.23, N7.93.

*2.5.10. 6-Bromo-3-{3-chloro-4-[4-(dimethylamino)-phenyl]-2-oxoazetidin-1-yl}-2-[2-(2,6-dichlorophenyl)amino]benzyl-quinazolin-4(3H)-one (**5j**)*

Yield 51%, m.p. 173–176 °C. IR (KBr): t = 3448 (NH), 2922, 2852 (CH_2), 1745 (C═O, azetidinone), 1682 (C═O, quinazolinone), 1615 (C═N), 751 (C–Cl), 576 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.85 (s, 6H, N(CH_3)$_2$), 3.28 (d, 1H, N–C*H*, J = 5.4 Hz), 3.39 (d, 1H, C*H*–Cl, J = 5.4 Hz), 3.56 (s, 2H, CH_2), 6.37–8.13 (m, 14H, Ar–*H*), 9.16 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 31.46 (*C*H_2), 42.78 (N(*C*H_3)$_2$), 57.37 (N–*C*H), 62.48 (*C*H–Cl), 112.87, 116.23, 120.53, 121.64, 123.12, 124.34, 124.55, 126.73, 127.21, 127.47, 128.19, 129.52, 131.21, 132.24, 135.37, 136.63, 137.19, 141.68, 146.21, 148.29 (Ar–*C*), 161.76 (*C*═O, quinazolinone), 162.32 (*C*═O, azetidinone),

Table 3 Antifungal activity of compounds **4a–k** and **5a–k**.

Compound	R	*C. albicans* ATCC 10231				Potency (%)
		Std.: amphotericine-B				
		U_H	U_L	S_H	S_L	
4a	2-NO_2	2	1	9	4	25.88
4b	3-NO_2	2	1	9	4	25.88
4c	2-OH	0	0	9	4	0
4d	4-OH	1	0	9	4	19.75
4e	2-Cl	2	1	9	4	25.88
4f	4-Cl	4	2	9	4	44.44
4g	4-OCH_3	4	2	9	4	44.44
4h	3,4,5-$(OCH_3)_3$	3	1	9	4	35.25
4i	2-OH-4-OCH_3	0	0	9	4	0
4j	4-$N(CH_3)_2$	1	0	9	4	19.75
4k	2-OH-4-$N(C_2H_5)_2$	1	0	9	4	19.75
5a	2-NO_2	3	1	9	4	35.25
5b	3-NO_2	2	1	9	4	25.88
5c	2-OH	0	0	9	4	0
5d	4-OH	2	1	9	4	25.88
5e	2-Cl	3	1	9	4	35.25
5f	4-Cl	5	3	9	4	56.03
5g	4-OCH_3	4	2	9	4	44.44
5h	3,4,5-$(OCH_3)_3$	3	1	9	4	35.25
5i	2-OH-4-OCH_3	1	0	9	4	19.75
5j	4-$N(CH_3)_2$	1	0	9	4	19.75
5k	2-OH-4-$N(C_2H_5)_2$	1	0	9	4	19.75

U_H: zone of inhibition of compound at 100 μg/ml; U_L: zone of inhibition of compound at 50 μg/ml; S_H: zone of inhibition of standard at 100 μg/ml; S_L: zone of inhibition of standard at 50 μg/ml.

164.47 (*C*═N) ppm. Anal. For $C_{32}H_{25}BrCl_3N_5O_2$ (697.84) calcd. C55.08, H3.16, N10.04. Found C54.96, H3.20, N9.98.

*2.5.11. 6-Bromo-3-{3-chloro-4-[4-(diethylamino)-2-hydroxyphenyl]-2-oxoazetidin-1-yl}-2-[2-(2,6-dichlorophenyl)amino]benzyl-quinazolin-4(3H)-one (**5k**)*
Yield 64%, m.p. 178–185 °C. IR (KBr): t = 3446 (NH), 3265 (OH), 2923, 2852 (CH_2), 1750 (C═O, azetidinone), 1680 (C═O, quinazolinone), 1606 (C═N), 760 (C–Cl), 582 (C–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.33 (t, 6H, $N(CH_2CH_3)_2$, J = 7.6 Hz), 2.84 (q, 4H, $N(CH_2CH_3)_2$, J = 7.6 Hz), 3.30 (d, 1H, N–C*H*, J = 5.5 Hz), 3.38 (d, 1H, C*H*–Cl, J = 5.5 Hz), 3.55 (s, 2H, CH_2), 5.65 (s, 1H, O*H*), 6.39–8.15 (m, 13H, Ar–*H*), 9.17 (bs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 14.73 ($N(CH_2CH_3)_2$), 31.53 (CH_2), 43.83 ($N(CH_2CH_3)_2$), 56.76 (N–*C*H), 65.28 (*C*H–Cl), 95.76, 104.34, 116.27, 118.76, 120.63, 121.50, 123.08, 124.26, 124.42, 126.62, 127.33, 127.55, 128.63, 129.44, 131.27, 132.23, 136.48, 137.29, 141.77, 146.16, 148.87, 156.45 (Ar–*C*), 161.67 (*C*═O, quinazolinone), 162.23 (*C*═O, azetidinone), 164.63 (*C*═N) ppm. Anal. For $C_{34}H_{29}BrCl_3N_5O_3$ (741.89) calcd. C55.04, H3.94, N9.44. Found C54.95, H3.98, N9.39.

2.6. Antimicrobial activity

The *in vitro* antimicrobial activity of compounds **4a**–**k** and **5a**–**k** were carried out by cup-plate method (Barry, 1976). Antibacterial activity was screened against two gram positive bacteria (*Staphylococcus aureus* ATCC 9144 and *Bacillus subtilis* ATCC 6633) and two gram negative bacteria (*Pseudomonas aeruginosa* ATCC 9027 and *E. coli* ATCC 25922), while antifungal activity was screened against fungi *Candida albicans* ATCC 10231 by measuring the zone of inhibition on agar plates at two different concentrations 100 and 50 μg/ml. Penicillin-G was used as a standard antibacterial agent whereas amphotericine-B was used as a standard antifungal agent. Microbial cultures were obtained from National Collection of Industrial Microorganisms (NCIM), National Chemical Laboratory, Pune. The potency of the compounds was calculated by using the following formula as per Edwin and Marion (1945).

$$\text{Potency} = \{\text{antilog}[(D/B) \times I]\} \times M \times F$$

where F = dilution factor = 1 (same dilution used for standard and test); M = potency of standard = 100; $I = \log S_H/S_L$; $D = (U_H + U_L) - (S_H + S_L)$; $B = (U_H - U_L) + (S_H - S_L)$; U_H = zone of inhibition of compound at 100 μg/ml; U_L = zone of inhibition of compound at 50 μg/ml; S_H = zone of inhibition of standard at 100 μg/ml; S_L = zone of inhibition of standard at 50 μg/ml.

3. Results and discussion

3.1. Chemistry

The title compounds, 6-bromo-2-[2-(2,6-dichlorophenyl)amino]-benzyl-3-substituted benzylideneamino-quinazolin-4(3*H*)-ones **4a**–**k** and 6-bromo-3-(3-chloro-4-substituted phenyl-2-oxoazetidin-1-yl)-2-[2-(2,6-dichlorophenyl)amino]benzyl-quinazolin-4(3*H*)-ones **5a**–**k**, have been synthesized according to the described process in Scheme 1. The structures of all the compounds were established on the basis of elemental analyses, IR, ^1H NMR, and ^{13}C NMR spectral data. The required benzoxazinone **2** was prepared by the cyclization reaction between 5-bromo anthranilic acid and 2-[(2,6-dichlorophenyl)-amino]phenyl acetyl chloride **1** using pyridine. The formation of the product was confirmed by a sharp band at 1740 cm^{-1} for C═O group along with a band at 1153 cm^{-1} for C–O stretching in the IR spectrum. Compound **2** was converted to quinazolin-4(3*H*)-one **3**, by its condensation reaction with hydrazine hydrate in methanol. The disappearance of the C–O stretching band at 1153 cm^{-1} and the presence of a sharp C═O stretching band at 1684 cm^{-1} instead of a C═O stretching band at 1740 cm^{-1} confirmed the formation of quinazoli-4(3*H*)-one. This was further confirmed by ^{13}C NMR spectrum, which showed C═O and C═N signals of quinazolinone at δ 161.2 ppm and δ 164.5 ppm, respectively. When compound **3** was treated with substituted aromatic aldehydes in the presence of glacial acetic acid as a catalyst, Schiff bases **4a**–**k** were formed, which were confirmed by the presence of strong –N═CH– stretching vibration of the Schiff bases at around 1630 cm^{-1} and ^1H NMR spectra showed a singlet at around δ 6.20 ppm due to one proton of the Schiff base. Further cyclization reaction of Schiff bases **4a**–**k** with chloro acetyl chloride in the presence of triethylamine as a catalyst at 0–5 °C gave the desired compounds 2-oxo-azetidinyl-quinazolin-4(3*H*)-ones **5a**–**k**. IR spectra of compounds **5a**–**k** showed strong stretching vibration at around 1750 cm^{-1} due to C═O group of 2-azetidinone. ^1H NMR spectra of **5a**–**k** showed a doublet at around δ 3.26 ppm and δ 3.37 ppm equivalent to one proton due to N–CH and CH–Cl of 2-azetidinone ring, respectively.

3.2. Antimicrobial activity

The results of antibacterial activity are shown in Tables 1 and 2. Schiff base derivatives **4e**, **4f**, **4g** and 2-azetidinone derivatives **5g** and **5h** exhibited good activities (50.88–52.88%) against gram positive bacteria *S. aureus* while compounds **4g** and **5g** displayed good activity (60%) against gram positive bacteria *B. subtilis*. Schiff bases as well as 2-azetidinones **4f**, **4g**, **4h**, **5f**, **5g** and **5h** showed good activities (58.24–61.54%) against gram negative bacteria *P. aeruginosa* whereas compounds **4g** and **5g** showed good activities (56.66% and 64.29%, respectively) against gram negative bacteria *E. coli*. The remaining compounds possess moderate to poor activities as compared to penicillin-G.

The results of antifungal activity are shown in Table 3. Schiff bases possess moderate to poor activities (19.75–44.44%) against *C. albicans* while 2-azetidinone **5f** showed good activity (56.03%) against *C. albicans*. The remaining 2-azetidinone derivatives exhibited moderate to poor activities as compared to amphotericine-B.

4. Conclusions

- Compound containing chloro and methoxy group showed good antimicrobial activity in most of cases.
- 2-Azetidinone derivatives were found active than Schiff base derivatives.
- Compound containing 4-dimethylamino and 2-hydroxy-4-diethylamino groups were found inactive against bacterial species.

- Compound **5f** which containing 4-chloro group showed good antifungal activity with potency of 56.03% against *C. albicans*.
- Schiff bases as well as 2-azetidinones possessed moderate to poor antifungal activity except compound **5f**.

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